Title page

A randomised controlled trial testing provision of fecal and blood test options on participation for colorectal cancer screening.

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Running title: Provision of a blood test in a FOBT screening program

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Abstract

Suboptimal participation is commonly observed in colorectal cancer screening programs utilising fecal tests. This randomised controlled trial tested if the offer of a blood test as either a "rescue" strategy for fecal test-non-participants or an upfront choice, could improve participation. 1800 people (50–74y) were randomised to Control, Rescue or Choice groups (n=600/group). All were mailed a fecal immunochemical test (FIT, OC-Sensor, Eiken Chemical Company) and a survey assessing awareness of the screening tests. The Rescue group was offered a blood test 12wk after FIT non-participation. The Choice group was given the opportunity to choose to do a blood test (Colvera, Clinical Genomics) instead of FIT at baseline. Participation with any test after 24wk was not significantly different between groups (Control: 37.8%, Rescue: 36.9%, Choice, 33.8%, $p>0.05$). When the rescue strategy was offered after 12wk, an additional 6.5% participated with the blood test, which was greater than the blood test participation when offered as an up-front choice (1.5%, $p<0.001$). Awareness of the tests was greater for FIT than for blood (96.2% vs 23.1%, $p<0.0001$). In a population familiar with FIT-screening, provision of a blood test either as a rescue of FIT non-participants or as an up-front choice did not increase overall participation. This might reflect a lack of awareness of the blood test for screening compared to FIT.

Keywords:

colorectal cancer; screening; fecal immunochemical test; circulating tumour DNA; FOBT

Early detection is critical to reducing mortality from colorectal cancer (CRC) and can be achieved through effective screening programs. Many countries have implemented organized, population-based, screening programs with fecal occult blood tests (FOBT), but participation rates can be poor (1-3) and need to be improved for screening to achieve its full potential as a public health strategy.

Previous work that focused on identifying and removing barriers to participation in fecal test-based screening suggests that a blood test could improve screening uptake, particularly for those who dislike fecal sampling (4, 5) or who have a benign, bleeding condition making completion of FOBT inappropriate (6). Research has confirmed that dislike of fecal sampling is a common reason for non-participation in screening (7), with one study finding that fecal tests were the least preferred of various testing options including colonoscopy, barium enema, sigmoidoscopy and virtual colonoscopy (8). Beliefs about CRC prevention, awareness of the tests and the benefit of screening (9), as well as test technology variables (10, 11, 9) are also likely to be relevant when designing screening programs.

Emerging molecular diagnostic assays offer the potential to detect circulating tumour DNA (ctDNA) in blood by detection of aberrantly methylated genes in CRC such as *SEPT9* (12). We have shown that the genes *BCAT1* and *IKZF1* are methylated with high frequency in colorectal neoplastic tissues (13, 14) and that methylation in these genes can be detected in the plasma of patients with CRC (15, 16). The methylated *BCAT1/IKZF1* blood test has comparable sensitivity to fecal immunochemical tests for hemoglobin (FIT) for detection of CRC, and better specificity (17). Use of these blood tests could circumvent fecal aversion or inappropriateness in the case of benign medical conditions causing bleeding, and therefore improve screening program participation.

To date, participation rates with blood or fecal tests have not been compared in a general population already familiar with fecal test-based, centralised screening program. It is important to understand whether a population that has been offered a fecal test would be prepared to screen with a blood test, particularly in those who have previously rejected the fecal test. A blood test could provide the possibility of engaging such non-participants. A conservative approach would have a screening blood test deployed within a screening program as a second line “rescue” strategy to engage those who reject the existing fecal test-screening method. Alternatively, it might be offered as an upfront choice. Understanding influences on participation, as well as test mode preferences, would provide useful information on how best to implement a blood test for CRC screening.

The primary aim of this study was to determine whether provision of a blood screening test, either as an up-front choice, or as a "rescue" offer to fecal test non-participants, within a mail-based FIT-based screening program would increase screening uptake compared to a standard screening program that only offers a fecal test. The secondary aim was to understand whether demographics, experience with screening or differences in anxiety about test sampling influenced preferences and choice.

Materials and Methods

Participants and study design

A random selection of people aged 50–74 years was provided by the Australian Electoral Commission for six electoral regions of South Australia. Each region was matched for gender and 5 year age bands. Study invitees were randomised into three groups (n=600/group) using a random number generator. The study groups were labelled as Control, Rescue and Choice.

The study consisted of two consecutive 12-week phases (Figure 1). In the first phase, all groups were invited to screen and were mailed a free FIT kit, with the Choice group also provided with the opportunity of arranging a blood test in place of using the FIT. In the second 12-week phase, the Control group received a further reminder to screen with FIT, the Rescue group were similarly reminded but also given information for arranging a blood test instead of the FIT, while the Choice group received no reminder.

Prior to the screening invitation, all invitees in each group were mailed an advance notification letter (18) alerting them to the importance of screening for CRC and advising them that they would shortly be sent an invitation to participate in a screening study, but were not informed of the study design. Individuals were provided with a phone number which they could use to opt-out from the screening offers if they had completed a screening test within the previous 12 months, or had a colonoscopy within the previous five years.

Ethical approval for the study was obtained from the Southern Adelaide Clinical Human Research Ethics Committee, with the study conducted in accordance with the Declaration of Helsinki. The trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry (trial number ACTRN 12615000972527). Written informed consent was obtained from all study participants.

Study Phase Interventions

Phase 1 (0-12 weeks) – initial screening offer

Two weeks following the advance notification letter, all study invitees who had not opted-out were mailed a screening pack in a design similar to that used by the Australian National Bowel Cancer Screening Program (NBCSP). The pack included an invitation letter and information sheet describing the study nature, a CRC screening information booklet, a participant details form, FIT kit and a survey for completion and return. The FIT kit included two sample collection tubes (OC Sensor, Eiken Chemical Company, Tokyo, Japan) and collection sheets, instructions on how to complete the test, and a reply-paid return envelope for the sample tubes and completed forms to be returned by post to the laboratory (Repatriation General Hospital, Daw Park, SA). Invitees were requested to sample from two different bowel motions at home and return the collected samples within 2 weeks. Samples collected incorrectly were not analysed, and a replacement kit was sent for the opportunity to repeat the test. Analysis of FIT collection tubes for hemoglobin concentration followed manufacturer instructions as previously described (19).

In addition, the Choice group was provided with written information in the invitation letter with details on how to call the helpline and request a referral for a blood test should they not wish to do the FIT. They were further informed that the blood test accuracy for CRC detection had a similar performance to the FIT in that it would detect at least 60% of colon and rectum cancers (17). Individuals opting for the blood test were sent an information sheet, a participant details form, a consent form, a list of blood collection centre locations, and a referral for the methylated *BCAT1/IKZF1* blood test (Colvera, Clinical Genomics Pty Ltd, North Ryde, NSW). Phlebotomy was arranged through blood collection centres (Healthscope Ltd), selected within the electoral regions. Blood was collected (18mL, K3-EDTA) and the extracted plasma was couriered to Clinical Genomics for assay of methylated *BCAT1* and *IKF1* as previously described (15).

Participation with FIT was recorded as return of the sample collection tubes, even if sampling was performed incorrectly. For the blood test offer, a phone call to request a referral was recorded as "interest in screening by blood test". Collection of blood was then registered as screening participation.

Within each group, if participation was not recorded within 6 weeks, a reminder letter was sent, consistent with our previous screening studies (11). After 12 weeks, study invitees in the Control and Rescue groups who had still not participated were eligible for Phase 2 (Fig. 1).

Phase 2 (13-24 weeks) – "rescue" offer

At 12 weeks, the Rescue group non-participants were mailed a letter inviting them to screen using the blood test. This invitation was identical to that provided to the Choice group invitees in Phase 1. The Control group non-participants were mailed a further reminder letter encouraging them to complete the previously provided FIT, or request a replacement if needed. Although the existing NBCSP protocol does not include a re-offer of tests after non-participation, we offered this to ensure comparability for analyses with the Rescue group invitees. All non-participants in Phase 2 were sent another reminder letter after a further 6 weeks (week 18).

Survey

The survey provided at invitation included the following elements:

1. *Demographic variables and past experience with screening*

Information on age, gender, marital status, education, employment status, country of birth, cultural identity, health insurance status and postcode were collected. The postcode enabled calculation of relative socioeconomic disadvantage (SEIFA) information (20) (a higher score indicates a relative lack of disadvantage). Information about previous experience with blood and fecal testing was also collected.

2. *Anxiety about samples involved in screening*

Blood-taking Anxiety and Fear of Needles were measured using an adapted version of measures developed by Deacon and Abramowitz (21). A Fecal Aversion scale was adapted for the study from Cole *et al* (9) consisting of 3 items for which agreement was scored on a 4 point scale from 1, strongly disagree to 4, strongly agree. An example item is "Collecting bowel motions is distasteful".

3. *Awareness of screening test types.*

The survey included questions asking respondents if they had ever heard of using a stool or blood test for screening in line with the first stage in the Precaution Adoption Process Model (22). Allowed responses were 'yes', 'no' or 'unsure'.

Data analysis

An improvement in participation rate of 10% for the intervention group was considered a meaningful difference, and it was expected that the control group would have a participation rate of approximately 50% based on our previous experience. A sample size of 600 per group (n = 1800 in total) provides more than 90% power to detect a difference in participation rates of 10% when assessed with a Chi-squared test of proportions and a 2-sided Type I error rate of alpha = 0.05.

Screening participation rates at 12 and 24 weeks were compared between groups using the Chi-squared test or Fisher Exact test. Sociodemographic characteristics were compared with one-way analysis of variance and chi-square tests for continuous and categorical variables respectively. Logistic regression analysis was performed to determine predictors of screening participation. A probability value less than 0.05 (two-tailed) was accepted as statistically significant. The reliability and internal consistency for adapted survey questions were determined with Cronbach's alpha coefficient.

Results

Characteristics of the Groups

The sociodemographic characteristics of the study population are shown in Table 1. There were no significant differences in any characteristic: Age $\chi^2(8) = 13.507$, p=0.096; Gender $\chi^2(2) = 2.110$, p=0.348; socioeconomic disadvantage $\chi^2(2) = 4.176$, p=0.126.

Participation in screening

Figure 1 shows the disposition of study invitees in each of the three groups and participation in response to each intervention and reminder letter over the 24 weeks. A small number of invitees in each group (n=3-15; total n=30) withdrew after receipt of the advance notification letter; the remainder (n=1770) were provided with screening invitation packs and included in subsequent analyses.

Figure 2 shows cumulative participation rates for each group by phase and according to the test used. Participation rates were not different between groups at the end of Phase 1 (χ^2 (2df)=1.02, p=0.601), and were still similar after 24 weeks (χ^2 (2df)=2.19, p=0.334). The re-invitation strategies applied to the Control and Rescue groups in weeks 13-24 resulted in increases in participation for the Control group of 3.6% (21/588; FIT only) and for the Rescue group of 5.3% (31/585; FIT or blood test, p>0.05). Participation with the blood test when offered as a Rescue strategy (23/353, 6.5%) was greater than when provided as an up-front option in the Choice group (9/597, 1.5%, χ^2 (1df)=17.08, p<0.001).

The proportion of participants who were female or male did not differ between tests; 52.1% (317/608) vs 47.9% (291/608) for FIT respectively (χ^2 (1df)=2.22, p=0.136) and 56.3% (18/32) and 43.8% (14/32) for the blood test (χ^2 (1df, Yate's corrected)=0.563, p=0.451) respectively. The age

distribution of participants is shown for each test in Table 2. Participation did not differ by age using FIT (χ^2 (4df)=4.10, p=0.393) nor for the blood test (but numbers were low; χ^2 (4df)=0.265, p=0.992). Participation with any type of screening test was less in the age group under 65y compared to those ≥65y (33.1% vs 39.3%, χ^2=7.143, p=0.008).

Total screening uptake was not associated with socioeconomic status score (expressed as a continuous variable, OR 1.000, 95% CI 0.998-1.001, p=0.765). Similarly, of those who completed FIT (n=608), socioeconomic status was not a significant predictor (OR 1.000, 95% CI 0.999-1.002, p=0.837), whereas there was a trend for those who completed the blood test (n=33) to be from the lower socioeconomic status areas. For each unit increase in socioeconomic status score, there was a 0.5% decrease in odds of completing the blood test, but this did not reach statistical significance (p=0.075).

Blood test request and participation

Table 3 shows the number of invitees in the Rescue and Choice groups who were given information for arranging a blood test and then attended a collection centre. A significantly greater proportion of the Rescue group participants requested the blood test compared to the Choice group (p<0.001) but only 23/40 (57.5%) of requesters from the Rescue group actually attended for the blood test compared to 9/10 of the Choice group (90%, Fisher test, p=0.073). Nonetheless, actual participation with the blood test remained higher in the Rescue group (Table 3). There were no differences in demographics between those requesting referral for the blood test without participating, and those who attended the collection centre (Supplementary Table 1; all p>0.26).

Relationship between test awareness, sample anxiety, past FIT-screening and participation

Surveys were completed by 560/1770 (31.8%) invitees. Irrespective of study group, 83.8% of survey respondents (469/560) subsequently completed a FIT test, 1.1% (6/560) completed a blood test and 15.2% (85/560) did not complete any test within the 24wk study duration. Survey completion rates were lower in males (40.5% *vs*. 52.6%, χ^2=6.53, p=0.011) and in those aged <65y compared to ≥65y (27.8% vs. 37.6%, χ^2=18.85, p<0.001). There was no significant difference between socioeconomic status of survey respondents and non-respondents (proportions of respondents and non-respondents in the most disadvantaged socioeconomic status groups were 37.3% and 38.7%, respectively; p=0.578). There were also no between-group differences in the proportions completing the survey or in the number of survey respondents who did the FIT (Table 4).

The majority of survey respondents were aware of the fecal test for screening (536/557, 96.2%), and had previously completed a FIT (476/538, 88.5%). In contrast, the majority (76.9%) of respondents were unaware of a blood test for screening (426/554; χ^2(1df)=471,9, p<0.0001)**,** although the majority had had blood taken previously by a health professional (502/548 responses, 91.6%).

The relationship between past participation in FIT-based screening and actual participation in this study, by intervention group, is summarised in Table 4. There was no between-group difference in FIT participation between those who had previously participated and those who had not previously completed a FIT. In contrast, experience in having completed any blood test prior to the study was significantly more likely in Rescue and Choice Groups (p=0.001).

Anxiety about sampling process and participation

There was no significant difference in Fecal Aversion (overall range 3-12) between those who returned a FIT within the study duration (n=433, mean 5.41, SD 1.91) and those who did not (n=82, mean 5.37, SD 2.06; t (513)=0.17, p=0.86). The Fecal Aversion scale had good internal consistency, with a Cronbach's alpha of 0.875 (n=515 respondents). Analysis of the impact of scores on the measures Blood-taking Anxiety, Fear of Needles and Fecal Aversion was not possible within the blood-test invitees given the very small number who utilised the test.

Discussion

In fecal-based screening programs, barriers to participation include fecal aversion and unsuitability of the test on medical grounds, such as presence of benign bleeding conditions (4, 6). A blood test for ctDNA might circumvent these two barriers. However, logistics of this approach, specifically attendance at a blood collection centre, might create a different barrier to test completion. This barrier is not seen with fecal sampling, which can be undertaken at home. Furthermore, public understanding of, and familiarity with, blood testing for CRC screening is likely to be poorer than for fecal sampling and impact on potential participation, regardless of whether blood tests are offered as an option or as a rescue strategy. Strategies to implement a blood test, and the resulting participation in a screening context in a country that uses mailed FIT for the centrally organised screening program, have not been previously investigated.

This study assessed two strategies for implementing a blood test within a mailed FIT-based screening program. The blood test used was one that assays for the ctDNA biomarkers methylated *BCAT1* and *IKZF1*, and which is known to detect approximately two-thirds of patients with CRC

(16, 17). We measured screening participation using a rescue strategy (offer of the blood test to FIT non-participants) and a choice strategy (as an up-front alternative option to FIT). We also tested relevant behavioral variables, awareness and aversion, to see if they related to test usage.

In this screening context, and judging on overall participation rates after 24 weeks, neither the rescue nor choice strategies improved test-independent participation rates. We observed only a small number of individuals completing the blood test. This is in contrast to the Australian research that found that when presented with a hypothetical choice of screening tests, the majority had a strong preference for a blood test compared with a stool test (79% vs 20%) (4). Likelihood of participating was significantly negatively associated with increased health system interactions, and the blood screening scenarios featured increased interactions (23). Thus, although people may indicate acceptance of blood testing, reported acceptance may not improve participation rates due to perceptions that the approach requires significant time commitment and logistical complexity. Moreover, reported intention to engage in a behavior does not necessarily predict actual behavior. A meta-analysis of 10 meta-analyses of the intention-behavior relationship conducted by Sheeran (24) indicated that intentions only explained 28% of the variance of future behavior. Despite this, we found that among those who requested information about the blood test, the majority attended blood collection. In the study design we provided multiple blood collection locations within each electorate region to provide convenient access to phlebotomy to reduce this as a barrier for screening.

In those that did complete the blood test, there was a trend towards greater uptake in those from lower socioeconomic status areas. The Australian CRC screening program, as well as other studies, report that participation with FIT screening is positively correlated with socioeconomic status (25, 26). Our finding may therefore have strategic implications for screening rollout, and targeted rescue strategies could be trialled. It is also likely that preference for FIT and blood test could differ by ethnicity. One study that compared screening test type preferences (colonoscopy vs blood test) found that there were racial differences (27). We were unable to analyse participation data in relation to ethnicity as this information was unavailable for the entire invited cohort.

Another obvious explanation for limited use of the blood test when provided in this context is the dramatic difference in awareness of the ability to screen with a fecal compared to a blood test (96% vs 23%). This difference in awareness was likely to affect perceived test efficacy; future research should measure trust in the screening technology and its influence on participation. It is intriguing that participation using the blood test was more likely when it was offered in a rescue strategy than

as an up-front option. This emphasises the importance of context when offering screening tests; the rationale for using the blood test may be clearer to someone failing to engage in the FIT, even when awareness of the fecal test was much higher. Nonetheless, paying particular attention to non-participants generates a response in itself and using a blood test to rescue non-participants is clearly preferred to FIT.

It is important to determine the best means to implement a new test into an existing screening program. We investigated both sequential offers and choice in the current study. In relation to the former, previous studies that show that sequential offers of different CRC screening tests can improve overall participation rates (28, 29). The second strategy raises issues about choice. Australian research shows that offering multiple options creates uncertainty (30), but it may also improve participation by allowing individuals to choose a test which aligns with their preferences (31). Given that most people of screening age are familiar with having blood taken, we believed that this option might reduce barriers associated with having to make a choice because familiarity can overcome perceived barriers (4). In addition, the offer of choice in screening modality has achieved significant support with the American Cancer Society strongly advocating for patients to be given the opportunity to make an "informed" choice of test (32). In the current study, the anticipated benefit of offering patients choice in decision-making about screening test (e.g., Indamoni et al. (33)) however did not lead to increased participation; no benefit was seen comparing participation at conclusion of Phase 1 between the Choice group and either the Control or Rescue groups. Surprisingly, only 1.5% of those who participated in the Choice group opted to receive the blood test. Neither the idea of an option or the nature of the option itself achieved better participation. There have been few previous studies examining the effectiveness of providing a choice in screening tests. None of them has resulted in enhanced participation when the choice is offered at the outset (34, 35). This is referred to as the "choice paradox" where allowing individuals to choose between screening strategies results in a lower participation rate instead of the expected improvement in uptake (36). Potentially the convenience of the home fecal test compared to the time and expenses associated with the requirement to attend for venesection over-rides the other influences. The blood test obviously added complexity to screening logistics because not everyone who requested a blood test referral attended a collection centre.

It might also be expected that anxiety about having blood taken or aversion to sampling feces might influence test choice as these have previously been identified as potential barriers, but in this study fecal aversion did not appear to account for completion or non-participation with FIT. The number of survey respondents was too small to allow assessment of anxiety about blood collection.

A strength of this study is that it is applicable to population-based organised-screening programs with FIT, a standard practice in many countries (1). However, this effect on participation is not necessarily relevant to personalised screening delivered through direct discussion with a health professional. Furthermore, in such settings, facilities for blood collection are likely to be close at hand and the more complex logistics of blood sampling are negated because a special appointment is not otherwise needed. The blood test is more likely to be taken up at a time when a person attends a health professional and further studies to investigate blood test rescue strategies in this context are warranted.

As the blood test was new, a sizable amount of documentation (nature, value and risks) was provided when the blood test was offered to achieve adequately informed consent. This was a limitation to the study and may have created information overload and lead to confusion in these groups resulting in blunted participation with the blood test. In addition, the provision of the survey prior to completion of the intervention could have added to this overload and compromised participation, however, such an effect would have applied to all groups. A further limitation was that not all groups within the study received the same number of reminders for screening participation. The choice group only received a reminder following 6 weeks of non-participation, to mimic the usual practice of the Australian National Bowel Cancer Screening Program; while the control and rescue groups received additional contact at the 12 and 18 week time points. A further reminder was unlikely to significantly change overall outcomes, but nonetheless it remains a study limitation. In addition, this study was conducted in the general population of Australia, where a sizable proportion of the population are known to be up-to-date with screening (37).

In conclusion, provision of a blood test either as a rescue of FIT non-participants or as an up-front choice to FIT, did not increase overall participation in a population familiar with FIT-screening offered in an organised program through a centralised mail-out. This might in part be due to convenience of sampling at home with FIT relative to the inconvenience of needing to attend for a blood test but lack of awareness of the blood test as a screening option may also be a contributing factor. Although the two tests have comparable sensitivity for cancers, the blood test has poor performance characteristics for adenoma detection (17), and therefore FIT should remain the first line test to be offered in screening programs. However, use of blood tests for screening are an appropriate rescue mechanism for those unwilling or unable to complete FIT for behavioral or medical reasons (6). Furthermore, the context in which the blood test is offered is important as it was taken up more often when offered as a rescue to non-participants than as a choice at the initial

invitation. It is possible that the blood test might prove more useful when offered in the context of personalised screening where health professionals are directly involved in the invitation and blood collection facilities are close at hand.

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References

1. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637-49.

2. Young GP, Rabeneck L, Winawer SJ. The Global Paradigm Shift in Screening for Colorectal Cancer. Gastroenterology. 2019;156(4):843-51 e2.

3. AIHW. National Bowel Cancer Screening Program monitoring report: 2016. Canberra: Australian Institute of Health and Welfare Canberra; 2016.

4. Osborne J, Wilson C, Moore V, Gregory T, Flight I, Young G. Sample preference for colorectal cancer screening tests: Blood or stool? OJPM. 2012;2:326-31.

5. Osborne JM, Flight I, Wilson CJ, Chen G, Ratcliffe J, Young GP. The impact of sample type and procedural attributes on relative acceptability of different colorectal cancer screening regimens. Patient Prefer Adherence. 2018;12:1825-36.

6. Symonds EL, Cock C, Meng R, Cole SR, Fraser RJL, Young GP. Uptake of a colorectal cancer screening blood test in people with elevated risk for cancer who cannot or will not complete a faecal occult blood test. Eur J Cancer Prev. 2018;27(5):425-32.

7. Worthley DL, Cole SR, Esterman A, Mehaffey S, Roosa NM, Smith A et al. Screening for colorectal cancer by faecal occult blood test: why people choose to refuse. Intern Med J. 2006;36(9):607-10.

8. Marshall DA, Johnson FR, Phillips KA, Marshall JK, Thabane L, Kulin NA. Measuring patient preferences for colorectal cancer screening using a choice-format survey. Value Health. 2007;10(5):415-30.

9. Cole SR, Zajac I, Gregory T, Mehaffey S, Roosa N, Turnbull D et al. Psychosocial variables associated with colorectal cancer screening in South Australia. Int J Behav Med. 2011;18(4):302-9.

10. Cole SR, Gregory T, Whibley A, Ward P, Turnbull D, Wilson C et al. Predictors of Re-participation in Faecal Occult Blood Test- Based Screening for Colorectal Cancer. Asian Pac J Cancer Prev. 2012;13(12):5989-94.

11. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen. 2003;10(3):117-22.

12. deVos T, Tetzner R, Model F, Weiss G, Schuster M, Distler J et al. Circulating methylated SEPT9 DNA in plasma is a biomarker for colorectal cancer. Clin Chem. 2009;55(7):1337-46.

13. Mitchell SM, Ross JP, Drew HR, Ho T, Brown GS, Saunders NFW et al. A panel of genes methylated with high frequency in colorectal cancer. BMC Cancer. 2014;14(54):doi: 10.1186/471-2407-14-54.

14. Symonds EL, Pedersen SK, Murray DH, Jedi M, Byrne SE, Rabbitt P et al. Circulating tumour DNA for monitoring colorectal cancer-a prospective cohort study to assess relationship to tissue methylation, cancer characteristics and surgical resection. Clin Epigenetics. 2018;10:63.

15. Pedersen SK, Baker RT, McEvoy A, Murray DH, Thomas M, Molloy PL et al. A two-gene blood test for methylated DNA sensitive for colorectal cancer. PLoS One. 2015;10(4):e0125041.

16. Pedersen SK, Symonds EL, Baker RT, Murray DH, McEvoy A, Van Doorn SC et al. Evaluation of an assay for methylated BCAT1 and IKZF1 in plasma for detection of colorectal neoplasia. BMC Cancer. 2015;15:654.

17. Symonds EL, Pedersen SK, Baker RT, Murray DH, Gaur S, Cole SR et al. A Blood Test for Methylated BCAT1 and IKZF1 vs. a Fecal Immunochemical Test for Detection of Colorectal Neoplasia. Clin Transl Gastroenterol. 2016;7:e137.

18. Cole SR, Smith A, Wilson C, Turnbull D, Esterman A, Young GP. An advance notification letter increases participation in colorectal cancer screening. J Med Screen. 2007;14(2):73-5.

19. Symonds EL, Osborne JM, Cole SR, Bampton PA, Fraser RJ, Young GP. Factors affecting faecal immunochemical test positive rates: demographic, pathological, behavioural and environmental variables. J Med Screen. 2015.

20. Australian Bureau of Statistic. Socio-economic Indexes for Areas: Technical Paper, 2016. Canberra. 2016.

21. Deacon B, Abramowitz J. Fear of needles and vasovagal reactions among phlebotomy patients. J Anxiety Disord. 2006;20(7):946-60.

22. Weinstein ND. The precaution adoption process. Health Psychol. 1988;7(4):355-86.

23. Zajac IT, Duncan A, Turnbull D, Wilson C, Flight I. Blood-based screening for bowel cancer may not resolve suboptimal screening participation in Australia. Aust N Z J Public Health. 2016;40(4):337-41.

24. Sheeran P. Intention-behavior relations: A conceptual and empirical review. European Review of Social Psychology. 2002;12(1):1-36.

25. AIHW. National Bowel Cancer Screening Program monitoring report: 2018. Canberra: Australian Institute of Health and Welfare Canberra; 2018.

26. Moons L, Mariman A, Vermeir P, Colemont L, Clays E, Van Vlierberghe H et al. Sociodemographic factors and strategies in colorectal cancer screening: a narrative review and practical recommendations. Acta Clin Belg. 2019:1-9.

27. Taber JM, Aspinwall LG, Heichman KA, Kinney AY. Preferences for blood-based colon cancer screening differ by race/ethnicity. Am J Health Behav. 2014;38(3):351-61.

28. Hol L, Kuipers EJ, van Ballegooijen M, van Vuuren AJ, Reijerink JC, Habbema DJ et al. Uptake of faecal immunochemical test screening among nonparticipants in a flexible sigmoidoscopy screening programme. Int J Cancer. 2012;130(9):2096-102.

29. Senore C, Ederle A, Benazzato L, Arrigoni A, Silvani M, Fantin A et al. Offering people a choice for colorectal cancer screening. Gut. 2013;62(5):735-40.

30. DeBourcy AC, Lichtenberger S, Felton S, Butterfield KT, Ahnen DJ, Denberg TD. Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. J Gen Intern Med. 2008;23(2):169-74.

31. van Dam L, Kuipers EJ, Steyerberg EW, van Leerdam ME, de Beaufort ID. The price of autonomy: should we offer individuals a choice of colorectal cancer screening strategies? Lancet Oncol. 2013;14(1):e38-46.

32. Volk RJ, Leal VB, Jacobs LE, Wolf AMD, Brooks DD, Wender RC et al. From guideline to practice: New shared decision-making tools for colorectal cancer screening from the American Cancer Society. CA Cancer J Clin. 2018;68(4):246-9.

33. Inadomi JM, Vijan S, Janz NK, Fagerlin A, Thomas JP, Lin YV et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med. 2012;172(7):575-82.

34. Multicentre Australian Colorectal-Neoplasia Screening Group. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. Med J Aust. 2006;184(11):546-50.

35. Segnan N, Senore C, Andreoni B, Arrigoni A, Bisanti L, Cardelli A et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst. 2005;97(5):347-57.

36. Taupin DR, Corbett M. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. Med J Aust. 2006;185(4):238-9; author reply 9.

37. Zajac IT, Flight I, Turnbull D, Young G, Cole S, Wilson C. Self-reported bowel screening rates in older Australians and the implications for public health screening programs. Australas Med J. 2013;6(8):411-7.

Table 1. Demographic characteristics of invitees.

Demographic variables	**Control (n=600)**	**Rescue (n=600)**	**Choice (n=600)**
Age (years)			
50-55	122 (20.3%)	123 (20.5%)	115 (19.1%)
56-60	110 (18.3%)	135 (22.5%)	115 (19.1%)
61-65	116 (19.3%)	102 (17.0%)	142 (23.6%)
66-70	130 (21.6%)	122 (20.3%)	108 (18.0%)
71-74	122 (20.3%)	118 (19.6%)	120 (20.0%)
Gender			
Males	309 (51.5%)	282 (47.0%)	309 (51.5%)
Females	291 (48.5%)	318 (53.0%)	291 (48.5%)
Relative socioeconomic disadvantage			
Most disadvantaged	212 (35.3%)	244 (40.6%)	226 (37.6%)
Least disadvantaged	388 (64.6%)	356 (59.3%)	374 (62.3%)

Table 2. Age distribution of participants for each test type.

Test type	**Total participants (n)**	**Age band**					**Median age (y)**
		50-55y (%)	**56-60y (%)**	**61-65y (%)**	**66-70y (%)**	**71-75y (%)**	
FIT	608	101 (16.6%)	113 (18.6%)	124 (20.4%)	143 (23.5%)	127 (20.9%)	64.5y
Blood	32	6 (18.8%)	7 (21.9%)	7 (21.9%)	7 (21.9%)	5 (15.6%)	62.7y

FIT- fecal immunochemical test.

Table 3. Requests for referral for a blood test and actual participation by intervention group. Rates are adjusted according to number of invitations sent.

	Rescue screening	**Choice screening**	**Significance**
Requested blood test referral	40/353 (11.3%)	10/597 (1.7%)	χ^2=41.49, p<0.001
Attended for Blood test	23/353 (6.5%)	9/597 (1.5%)	χ^2=17.09, p<0.001
Proportion of requesters who attended.	23/40 (57.5%	9/10 (90%)	Fisher p=0.073

Table 4. FIT screening participation by previous screening for CRC with FIT, by intervention group

Participation	Control	Rescue	Choice	Significance
Total survey respondents	207/588 (35.2%)	176/585 (30.1%)	177/597 (29.6%)	χ^2=(2)=5.2 p=0.074
Survey respondents who completed study FIT	173/207 (83.6%)	152/176 (86.4%)	144/177 (81.4%)	χ^2(2)=1.63 p=0.442
Survey respondents who completed study blood test	N/A	3/167 (1.7%)	2/177 (1.1%)	χ^2(1)=0.004 (Yates) p=0.948
FIT knowledge and history[a]:				
Survey respondents who were aware of FIT prior to the study	195/205 (95.1%)	171/176 (97.2%)	170/176 (96.6%)	χ^2(2)=1.18 p=0.556
Survey respondents who had completed a FIT prior to the study	172/196 (87.8%)	150/171 (87.7%)	155/171 (90.6%)	χ^2(2)=0.979 p=0.613
Survey respondents who had completed a FIT prior to the study AND completed the study FIT	145/172 (84.3%)	131/150 (87.3%)	128/155 (82.6%)	χ^2(2)=5.63 p=0.060
Blood test knowledge and history[a]				
Survey respondents who had completed any blood test prior to the study	175/204 (85.8%)	164/175 (93.7%)	163/169 (96.4%)	χ^2(2)=15.2 p=0.001
Survey respondents who had completed any blood test prior to the study AND completed the study blood test	N/A	1/164 (0.6%)	2/163 (1.2%)	χ^2(1)=0 (Yates) p=0.996
Survey respondents who were aware of a blood test for CRC screening	48/206 (23.3%)	38/175 (21.7%)	42/173 (24.3%)	χ^2(2)=0.329 p=0.848

[a] Numbers of responses do not correspond to total number of surveys completed due to missing data.

CRC- colorectal cancer; FIT- fecal immunochemical test.

Figure legends

Figure 1. Study design and subject disposition**.**

FIT: fecal immunochemical test

Figure 2. Cumulative participation for each group after 12 and 24 weeks, according to test type.

FIT- fecal immunochemical test.

Figure 1

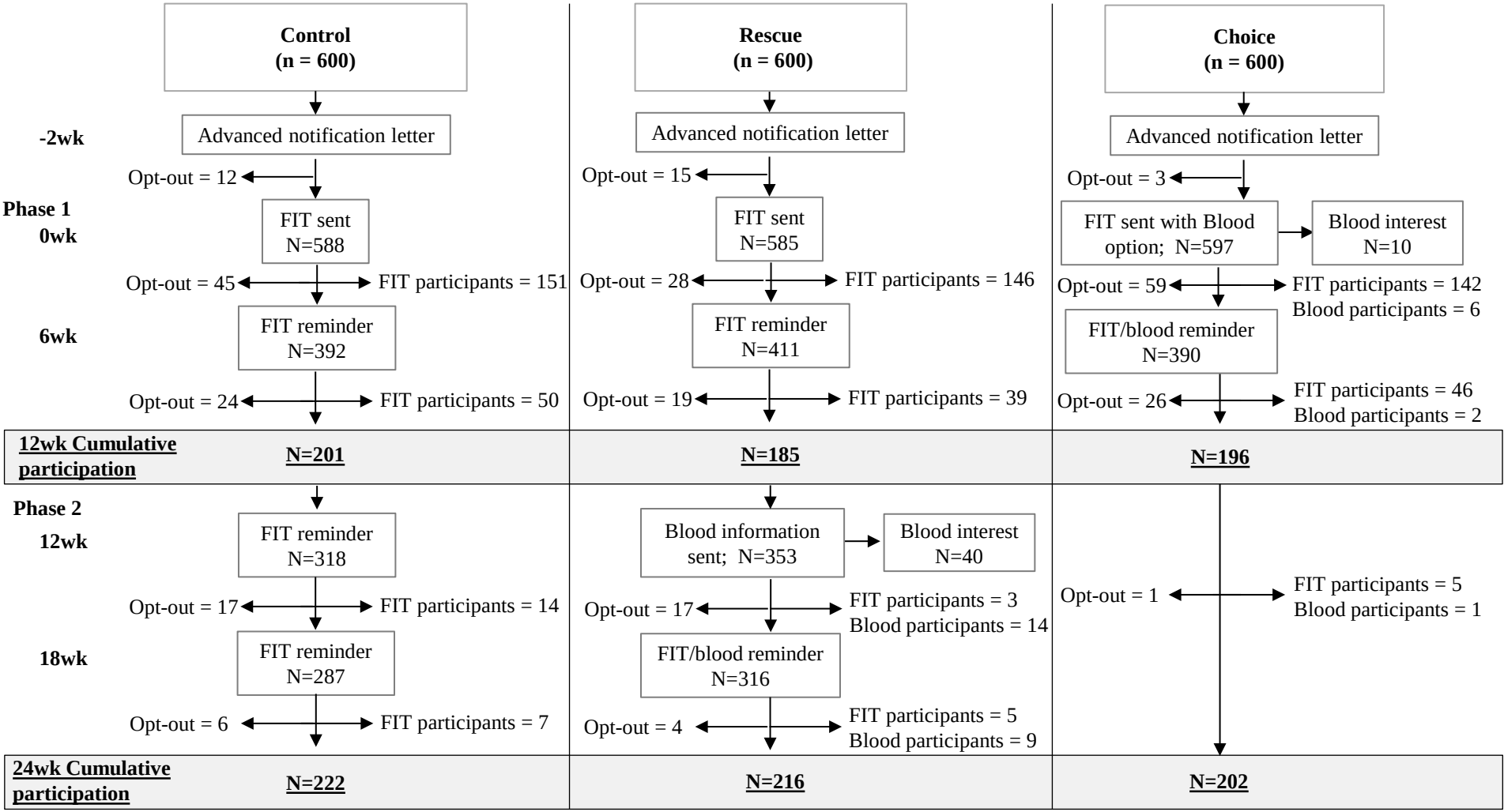
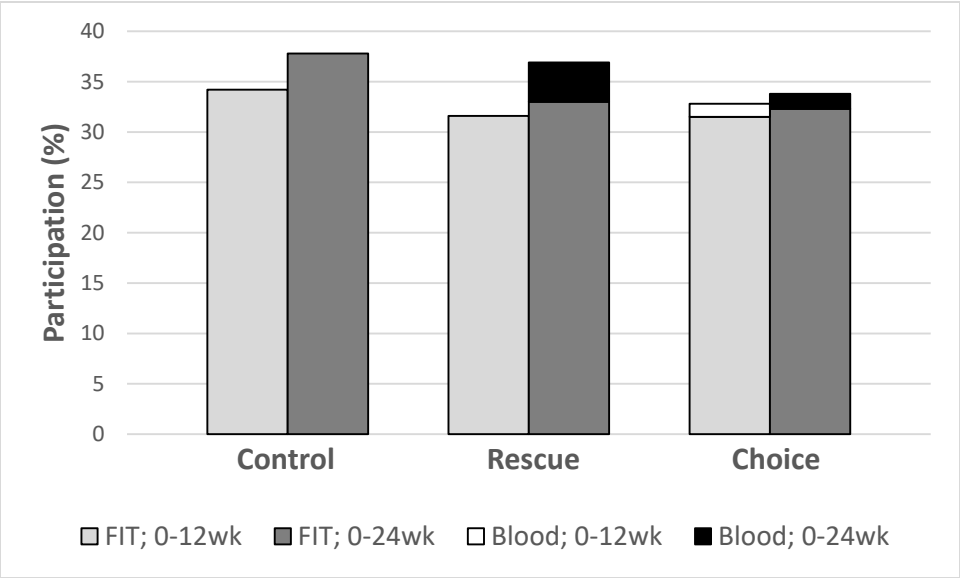


Figure 2



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